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An Address

ENTITLED

ARE THE PROBLEMS OF CANCER INSOLUBLE?

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Gentlemen,—Referring to du Bois-Reymond's discussion of the limits to physiological inquiry, Mach, in his "Analysis of the Sensations," points out that those problems which are insoluble from their very nature should be outside the domain of scientific thought. He suggests that their insoluble nature depends on the form in which they are stated—depends, in short, on an erroneous formulation. Rational thought must devise a re-statement of such problems in a way that makes their investigation profitable. More than other problems of medicine, the problems of cancer present a varying facies, according to the number, the variety, and the nature of the facts which we take into our purview in attempting to formulate them, and the conflicting standpoints of different investigators are the natural result. Experience and discussion have, however, already provided for the proper formulation and solution of some of those problems; but the history of the investigation of cancer presents many instances of problems still baffling solution because, as I believe, having been originally formulated on insufficient data, they have been wrongly formulated. Nevertheless their direct solution continues to be freshly attempted.

I propose to indicate my present conceptions of some of the problems of malignant new growths and the means by which their solution is being attempted. I shall re-state some of the problems which have long baffled solution in a form which makes their investigation profitable and their solution more hopeful. I shall express my opinions on the progress made towards the attainment of these ends as definitely as possible, and in reply to any criticism that I am not dogmatic enough, I shall contend that the investigation of cancer has suffered, and suffers to-day, from a too great readiness to hold dogmatic opinions on a subject of which we know so little and regarding which hitherto unsuspected facts have accumulated in recent years and are still accumulating.

Some three years ago the investigations of the Imperial Cancer Research Fund commenced. Those actively engaged in the task essayed to grapple with the disease, not as a problem of human pathology only, but as a comparative biological problem, and one requiring experimental treatment. Dr. J. A. Murray and myself have striven to place the exact knowledge of the nature and the incidence of the disease on a basis commensurate with its ramifications in men and animals. For, on the one hand, those facts which were matters of common knowledge to the medical profession were drawn from an extremely narrow field of investigation—viz., the study of the disease in man ; and, on the contrary, the hypotheses explaining them ranged over the full field of biological knowledge and speculation. To preserve an attitude sufficiently free from bias was no easy matter, because all coördinated investigation must be conceived in terms of a working hypothesis of some sort.

Older Hypothetical Explanations of the Nature and Growth of Cancer.

At that time various hypotheses were prominently before the medical profession—three especially contested for favour. In the Cohnheim hypothesis and its variants an embryonic origin was postulated, and to the minds of many the only alternative to an awakening of latent powers of growth in "embryonic rests" was the acquisition of new powers of growth by adult differentiated tissue. What was the amount of growth requiring explanation? It was the amount which sufficed to cause a patient to succumb to cancer and the explanations were formulated accordingly. The energy with which growth proceeds

showed no diminution up to the time of death and was loosely described as "limitless." How was this amount of growth to be elicited in either embryonic or adult tissue? Various forms of stimulus—*e.g.*, chronic irritation—were suggested. These suggestions were held to be an unsatisfactory answer to a question which the third hypothesis attempted to dispose of by assuming the intervention of a parasite to elicit the necessary power of growth.

The supporters of the two hypotheses first mentioned were not very active, partly owing to the absence of new facts to argue from and partly from the necessity for testing the fresh evidence brought forward in support of the parasitic hypothesis. The view that cancer was an infective disease directly transmissible from individual to individual was in favour in France and also in Germany, where the statistical results of a census of all the cases of cancer recorded on a definite day throughout the German empire had been adduced in its support for the first time. At home, on the Continent, and in America, most of the serious investigations were being directed to proving or disproving this hypothesis, although some suggestive work was being done bearing on the possible embryonic nature of tumours.

In regard to the hypothesis of infection, discussion chiefly centred around the interpretation of the increase recorded in the number of deaths from cancer, the apparent endemic occurrence of the disease, and the nature of certain bodies—the alleged parasites—frequently found in cancer cells, the best defined being those described by Plimmer in cancer of the breast. With the exception of the work done by Shattock and Ballance and some doubtful observations by Hanau, Moreau, and L. Löeb, only haphazard efforts * to prove or disprove the possibility of transmitting cancer experimentally had been made and the results were contradictory and wholly unsatisfactory. Anyone tackling the problem and seeking an explanation of the frequency of cancer, found himself obliged to sift the evidence for and against the view that cancer was directly communicable by infection. More recently, indeed just a year ago, a distinguished surgeon anathematised the bedclothing and the discharges of cancer patients as dangerous sources of infection.

The causative influence of geological formation, of soil, of climate and diet, of dwelling near rivers and trees, all found advocates. Civilisation even was blamed for calling cancer into being; the negro

* Jensen's and Borrel's investigations had not then been published.

in his native Africa was said to be free from cancer ; the negro of America was known to be prone to it. The veterinary profession had shown that all the forms of cancer occurred in domesticated mammals ; but medical men alleged, or were unable to disprove, that this was due to contact with man. Wild animals were said to be free from it. The evidence for its occurrence outside the mammals was regarded with the greatest distrust. Doubts were even expressed as to the identity of the disease in man and animals, although in 1899 Professor (now Sir) J. McFadyean had protested against the assertion of a distinguished member of the medical profession that cancer was a disease peculiar to man.

The Investigation of Cancer still in a State of Confusion and Error.

The confusion of opinions and conflicting statements of fact were disconcerting in the extreme to the mere medical man seeking guidance. The chaotic state of the whole matter was emphasised by the absence of any criteria serving as guide-posts in the wilderness of fact and fiction. Obviously where so much divergence of opinion was possible, many of the matters under discussion were open to ambiguity of interpretation or insufficiently supported by accurate observation. Investigation was hampered by the need for paying heed to a mass of disorderly details without any more obvious relation to one another than could be found for them in the imaginations of a multitude of authors wildly guessing at truth and formulating the problem they sought to solve in terms fitted less to the facts than to the solutions advanced. Truly there was, and is, need for work, much work and accurate observation, to cope with the flood of speculation and to elevate the investigation of cancer from the kind of "Tom Tiddler's" domain it had become and unfortunately still remains. From the outline I have given, it will be evident to you that we had to attempt to solve not one but many problems associated with cancer.

Organised Attempt to Systematise Investigation.

Those responsible for the institution of what is now the Imperial Cancer Research Fund foresaw that only a very far-reaching scheme of inquiry, backed by the most disinterested supervision possible—that of the Royal Colleges of Physicians and Surgeons—would suffice

to clear the ground. With the approval of the executive committee I determined to pursue five preliminary lines of inquiry covering most of the points at issue discussed above and affording means for submitting cancer to experimental study. In the first place it seemed essential: (1) to define the extent to which cancer occurred throughout the civilised and uncivilised races of man; (2) to determine the extent to which it pervaded the animal kingdom outside of the domesticated animals; (3) to ascertain whether the disease were transferable; (4) to demonstrate that any experimental observations made were made with cancer in all ways comparable to that found in man and to show the advantage of undertaking the study of specific problems in the animals best suited to their investigation *; and (5) the important deductions derived from statistics and their conflicting nature, together with the need for their valuable aid in furthering the zoological and biological lines of investigation, made it imperative to inquire into the uses to which statistics could be properly put and to ascertain the reliability of the clinical and pathological data on which they must be based. In this connexion the higher incidence of cancer in old age required special attention as a comparative biological problem; its statistical importance had long been recognised by accurate statisticians and most fully emphasised by Newsholme.

These preliminary lines of inquiry being objective in nature they permitted of investigation fairly free from bias. In their early stages they bore less on the nature of the disease and more on the value of existing knowledge and the elucidation of the relation of known facts to one another. I shall not weary you with details of the organisation † necessary for the conduct of those five lines of preliminary inquiry in

* *E. g.*, for the study of minute cell structures the amphibia have long been classical objects. The study of the cell of malignant new growths in the amphibia has been of the greatest value to us. The same group, owing to the power of regeneration, amounting even to the regeneration of entire limbs in some species, affords opportunities for studying the alleged analogy between the growth of cancer and the growth of tissues in reparative processes to replace defects. Up to the present, however, malignant new growths have only been successfully propagated in the mouse which has been found to be well suited for the experimental study of many features of cancer.

† We have elsewhere acknowledged our indebtedness to Government departments, London hospitals, medical and other officials of the Colonies and India, and to many collaborators at home and abroad, to Borrel, Jensen, Miss Plehn, and Pick especially who have worked independently on single lines of inquiry, similar to, or identical with, some of those mentioned above.

such a way that they formed parts of one coördinated investigation, the results of which will, I hope, show you that during the past three years many contradictions have been resolved, fallacies have been exposed, new facts have been elicited, the experimental method of investigating cancer has been placed on a sure and comparative basis, and the whole field of inquiry narrowed.

Ethnological and Zoological Distribution.

The energy of medical and other Colonial officials speedily led to the discovery of cases of cancer in native races of mankind hitherto supposed to be exempt, dwelling in parts of the world remote from European civilisation. Where, in the first instance, the disease was not found, cases have since been brought to notice. The inhabitants of Japan and China suffer from cancer, and upwards of 1000 cases have now been reported from the numerous native castes coming under the observation of European medical officers in India. The Danish Government informed us of its occurrence in the Arctic regions. The hearty response of the veterinary profession to the appeals addressed to them brought a surprising amount of material from domesticated mammals and some from wild animals in activity. One of our earliest cases was a carcinoma mammæ in a wild mouse. Malignant new growths were obtained from birds (tame and wild), some from fish—*e. g.*, from trout in hatcheries and from carp, also from marine fish living in a state of nature. Independently of us, Dr. Pick of Berlin described cases of malignant new growths in a fowl, a giant salamander, and in trout, the last having been originally recorded by Miss Plehn. A large tumour in an oyster, described as long ago as 1887, has been brought to our notice, and efforts are being made to find out its true nature.

The information on all the above lines continues to accumulate, and the search has been taken up in widely separated parts of the world. A few weeks ago Sir William McGregor forwarded a specimen of what is probably a malignant new growth in a codfish caught off Newfoundland, and Dr. Smallwood of Syracuse, U.S.A., sent us specimens of a new growth in a frog which we find is a columnar-cell carcinoma infiltrating the kidney. Recently Professor Welsh of Sydney, New South Wales, has also noted the occurrence of cancer in an aged lioness, an old tigress, and in a marsupial; likewise another growth in a frog. Dr. Pick continues to augment our knowledge of malignant

new growths in fish. His account of a painstaking investigation of carcinoma in trout aroused great attention last month at the Berlin Medical Society. Many of Dr. Pick's hearers went to the meeting still doubting the existence of such things. It soon became probable that all races of mankind were liable to cancer and likewise all vertebrate animals *, whether living in captivity or in a state of nature. To this general statement there is still one exception which we have pointed out before : a true malignant new growth has not yet been described in a reptile, but evidence was bound to be late in coming in the case of some groups, and there is no obvious reason why reptiles and invertebrates should not also suffer from cancer. There are, of course, difficulties in obtaining trustworthy data on its relative frequency either in native races of man or in animals.

Identity of Cancer in Men and Animals.

I illustrate some of the facts alluded to by slides showing carcinoma mammæ, malignant adenoma of the mammæ, squamous-celled carcinoma of the jaw, adeno-carcinoma of the small intestine, &c., in the mouse (tame and wild) ; carcinoma and malignant adenoma in salamander and in frog, also in the trout, codfish, gurnard, and some examples of sarcomata; from which you will see that the histological lesions characteristic of the disease throughout the vertebrates are identical with those characteristic of the disease in man †.

Constant Association with Old Age in Men and Animals.

I must, however, also tell you that cancer has the further remarkable common feature that in animals it has the same higher incidence in old age and therefore the same relation to the duration of life as in man, which involves that in animals with a shorter life tenure, the period of relative immunity is correspondingly shortened. Within the limited compass of the life of a mouse (three years) there are condensed the vital activities which in man may occupy more than half a century

* In this connexion we do not rely on sarcomata alone, which in animals may be closely simulated by other little known processes.

† We have refrained from detailed pathologico-anatomical description of tumours in lower animals because to have done so would have been to forsake the main purpose of our investigations, and Dr. Pick had taken up the subject in a most able manner. Where the tumours have been the starting-point for experiments their pathological features have been carefully studied and described.

and all series of events are correspondingly shortened. The association of cancer with old age is the only factor known to be constantly associated and intimately bound up with the processes responsible for the development of cancer in man and animals.

Limitations to Transmission and its Unique Features.

With apparent identity in the nature of a disease of such universal occurrence we were face to face with a new aspect of the old problem, Was it transmissible? Did an infective agent entering the body from without link together the sporadic cases so widely distributed in the animal scale from civilised man to marine fish living in a state of nature? The surmise was quickly arrived at that external factors such as habitat, food, and conditions of life generally played little, if any, direct part in causing a disease showing constant and unique characters in organisms so divergent. The influence of such inconstant external agencies is probably a mediate one as contrasted with the direct and constant association of cancer with old age. The essential factor or factors appear to be properties common to the cells of all the divergent organisms prone to the disease, and therefore the time of its appearance merely obeys the laws which set different limits to the compass of life. This conclusion would have been, perhaps, premature if drawn from the evidence of ethnological and zoological distribution alone. Concomitantly, however, the results of some of the other preliminary lines of inquiry showed that civilised man's responsibility for the occurrence of cancer in native races and domesticated animals was in all probability limited to providing them with an opportunity for reaching the "cancer ages." To the newly ascertained wide occurrence of the disease were also added: (1) the knowledge of the still more astonishing limitations to its transmission; and (2) the discovery that cancer possessed powers of continued growth after the death of the original host unparalleled either by organisms or tissues in the vertebrate kingdom. We have attempted the experimental transmission of the disease on a most extensive scale. In mice alone we have performed upwards of 10,000 experiments. We have obtained incontrovertible evidence that the disease is only readily transmissible from one individual to another of the same species or even of the same race. But to this restriction under favourable experimental conditions there are added yet others, so that its transmission naturally from one individual to another is a very improbable contingency; a conclusion

supported by the negative results of numerous experiments in which animals suffering from cancer have been housed with healthy animals.

I show you a series of slides illustrating the sequence of events when cancer is successfully inoculated from one animal to another. You will observe how a few parenchyma cells retain their vitality and continue to divide and multiply, giving rise to large tumours at the site of inoculation. On the contrary you will notice the rapid degeneration of the supporting tissues and blood vessels forming the stroma. They have not the vital powers of the cancer cells; they die and are supplied afresh, each time a piece of tumour continues to grow after being transferred to a fresh host. Nevertheless the new stroma assumes the distinctive features of the original stroma of sporadic tumours differing among themselves. The new tumours are therefore exactly like the original ones. Extensive metastases may form in the lungs, and you will observe that the growth of such transplanted tumours is either expansive or infiltrative, according to the site in which they are growing. Cancer thus artificially growing has all the properties of cancer as it occurs sporadically, even to the difficulty of discovering any specific symptoms of its presence. This identity is well illustrated by the behaviour of two growths in the walls of the small intestine. The appearances and mode of spread, from the mucous membrane towards the peritoneal surface, in the sporadic growth are duplicated in the invasion of the small intestine from the peritoneal surface by a growth following an intraperitoneal inoculation. The metastases in the lungs and the infiltration of the liver, kidneys, and diaphragm yield all the evidence necessary to make the demonstration complete.

Propagation succeeds as well in young animals as in old—perhaps better. Thus, although old age is constantly associated with the origin of cancer, it is not a necessary condition for the growth to continue when once it has started. Growth occurs in a large percentage of all the animals of the race used, and by re-inoculating those in which failure takes place in the first instance tumours can subsequently be obtained. Within one race there is little, if any, evidence of idiosyncrasy or varying suitability of the soil, as it were, and experiments show that success and failure are determined almost, if not entirely, by factors within the tumour cells themselves.

The facts I have been relating refer to the mouse, the only animal in which carcinoma has been successfully propagated. A mouse cancer will only grow in other mice, that of a tame mouse only well in other

tame mice of the same race, and that of a wild mouse only in another wild mouse of the same race. The cancer of a tame or wild Danish, German, or French mouse grows with difficulty, or not at all, in the corresponding race of English mice. It has been absolutely impossible to get cells from a mouse tumour to grow in any other species of animal. The outstanding features in the artificial transmission of cancer are therefore : (1) the great difficulty of transmission as contrasted with that of the known infective diseases ; (2) the continued vitality of the cancer cells as opposed to the death of the stroma cells and renewal of the stroma by the reaction set up in the tissues of the host at each re-inoculation ; (3) the cells descended from any one sporadic tumour, although apparently undifferentiated (embryonic), retain constant properties determining the specific nature of the stroma freshly supplied at each inoculation ; (4) the importance of unsuspected subtle differences in different races of mice sufficient to determine success or failure and, *per contra*, the unimportance of changes associated with age and other natural processes in the life cycle of the individuals of any one race when once cancerous growth has started ; and (5) the contrasts established between the transmission of cancer and all known processes of infection.

The contrast between the transmission of infection and the propagation of cancer is worthy of the serious attention of all those brought into contact with patients suffering from the disease or engaged in its investigation. The degeneration of the stroma of cancer on inoculation from one animal to another illustrates also what happens to the tissues of a tuberculous nodule if they be used to transmit tuberculosis to another animal ; they degenerate but they hand on the tubercle bacillus to the tissues of the new host, and these becoming infected, themselves exhibit the peculiarities of the disease. The experimental transmission of cancer means the continued growth of the tumour cells of one animal in a succession of other animals. The tissues of the new hosts do not acquire any cancerous properties ; they merely react to the presence of the cancer cells and supply them with nourishment. The process is fundamentally different and distinguishable from all known processes of infection. The transference of cancer cells from one mouse to another, therefore, affords them an opportunity for continuing to grow in a succession of animals. Jensen's tumour is growing to-day with undiminished energy four years after the death of the mouse in which it arose, and therefore for a period of one year longer than a mouse lives. In our own experiments

growth has proceeded in some 3000 mice successively, all of which are now dead, yet the tumour cells themselves are multiplying in other mice as actively as ever and producing enormous masses of tissue. The power of proliferation in this and four other tumours stands in no relation to the normal length of life, nor to the limits set to the growth of a mouse. In describing the artificial propagation of cancer, Dr. Murray and I have pointed out that it is a phenomenon unparalleled in the vertebrates and is a truer measure of the nature of the growth than that formerly known, which terminated in the death of a patient and itself ceased at that death. The experimental study of "expansive" and "infiltrative" growth shows that there is no essential difference between them. What is understood by the "malignancy" of a tumour is but a manifestation of the power of growth: a conclusion to which Ehrlich and Apolant have recently given confirmation.

General Conclusions from the Ethnological and Zoological Distribution, the Age Incidence, the Nature and the Limitations to the Transmission of Cancer.

Such is the difficulty of transmitting cancer from the tame mice of one country—*e.g.*, France or Germany—to the tame mice of England and the all but absolute impossibility of transmission from tame mice to wild mice, that I venture to assert that the prevalence of cancer among the negroes of America was not brought about by contact with cancer-infested white men. Cancer was inherent in the negroes when they were shipped from their native Africa, where it probably existed, as it still does to-day, in natives remote from civilisation. Nor has the white man been the focus from which the disease has spread throughout the vertebrate kingdom. The study of the limitations to the transmission of cancer shows that cancerous tissue possesses properties more specific to, and distinctive of, a species than any of the criteria by which the zoologist separates one species from another, or than the differences which the "precipitin test" has revealed between the blood of even nearly allied animals. Sporadically the disease arises *de novo* in each organism attacked and appears to be a process to which the tissues of the most divergent organisms are liable in the old age period of life. The only alternative is to postulate that each species, race, and even tissue, has got its cancer, or rather cancers, which are handed on from generation to generation like some family heirloom. This assumes

that cancers are themselves organisms implanted from individual to individual; that they are specific to the species, or even race, whose vitality they sap, and directly descended from some primeval cancer which started in remote geological ages. The supposition is entirely irrational and is disproved by the fact that cancer is constantly a disease of old age, whereas old age is not necessary for the transmission and growth of cancer; there is therefore no reason why cancer, transmitted as supposed, should not prefer youthful animals, instead of being increasingly frequent as age advances. This *reductio ad absurdum* is but one demonstration of the value of the comparative and experimental method of studying cancer.

In the light of the knowledge we now possess many of the problems that faced us three years ago have been solved and many of the confusing statements to which I have drawn attention cease to be worthy of serious consideration. The occurrence of cancer in codfish off the Banks of Newfoundland may not show that icebergs and fogs cause cancer, but it does show that dwelling in the neighbourhood of trees, or on a clay soil, living under the influence of civilisation or indulgence in alcohol, are not indispensable to the appearance of cancer. Time prevents me adding many facts to those I have laid before you. I can only allude to the valuable aid the statistical investigations have been to the others, and state that the minute study of the prolonged artificial propagation of cancer shows that the energy and the amount of proliferation fluctuate from causes inherent in the cells themselves. This study led us to discard, as being incompatible with the facts, the working hypothesis that growth might be maintained by the intercalation of heterotypical mitoses (like those of reproductive tissue), followed by nuclear fusion. In our investigations we have obtained evidence against all the explanations yet advanced as to the cause and nature of cancer, proof that cancer cells have not reverted to an embryonic undifferentiated state, or that the growth and ceaseless cell division of cancer resemble the intermittent growth and cell division of reproductive tissue, or that the artificial propagation of cancer resembles the grafting practised by horticulturists in the propagation of plants and trees. Thus at present any attempts directly to ascertain the cause and nature of cancer are surrounded by so many sources of fallacy that to my mind they remain to-day as unprofitable as they have been in the past. The attempt to *produce* cancer experimentally—*e.g.*, by chronic irritation—for what form of chronic irritation is constant throughout the vertebrate scale?—is also surrounded with great difficulty, not the

east part of which is the liability apparently inherent in all animals to acquire cancer in old age.

The constant association of cancer with old age suggests a direct attempt to ascertain the nature of the connexion. But such a direct attack is unprofitable because it at once opens up the bigger problem, What constitutes senility itself? This is a problem at present beyond our powers. There has long been indirect evidence that the connexion between senescence and cancer was local and not constitutional. Otherwise multiple primary growths would be the rule and not the exception. Our own observations show that the influence of age is active in relation to the origin of cancerous growth and not in relation to its continuation ; for cancer can be propagated almost better in young than in old animals. If it be permissible to formulate the association of cancer with old age in other terms, one may say that tissues which become cancerous alone escape the consequences of the senescence to which organisms as a whole succumb, or, that if cancerous tissues are also prone to succumb to senescence, they are able to recover from it. Stated in either way, the association of the origin of cancer with old age becomes a problem to be attacked after those formulated below with reference to the continued growth of cancer have been solved.

The artificial propagation of cancer tells us nothing directly as to the origin of cancer; it only indicates that the distinctive characters of any single malignant new growth, once acquired, are probably permanent, for under artificial propagation different carcinomata of one organ (the mamma) retain their individual characteristics. They are not convertible into one another nor do they merge into a common type. Artificial propagation gives the opportunity of studying many of the properties of malignant new growths in detail with a thoroughness unattainable in the case of sporadic tumours. It has already proved the inadequacy of the standards by which an anthropocentric pathology has attempted to measure the proliferation and to probe the nature of cancer. The true measure of that proliferation has not yet been arrived at. Its study suggests what appears at first sight to be a series of new problems, but may really be restatements of old ones—viz., Why is the amount of the growth of cancer relatively greater than that of any vertebrate organism ? Are growth and cell division always progressive ? Is cancer subject to a process of natural decay, or if not, how is its energy of growth and assimilation maintained ? To all these questions it should be possible to obtain a definite answer with

the means at our disposal, and once they have been answered the original problem, so long the object of futile direct attack, will present itself in another form more approachable than the old problem, "What is the cause of cancer?" has proved to be.

Competitive Research and Coördinated Investigation.

In conclusion, I feel it to be my duty to call attention to the risks attending the state of transition through which the investigation of cancer is passing at present. On the one hand, a change has come over the status of the actual investigators. A few years ago the investigation of cancer attracted *voluntary* workers only and almost, if not entirely, from the medical profession. To-day we have an increasing number of laboratories springing up all over the country and they are, or will be, provided with staffs *obliged* to investigate cancer and to devote their whole time to this duty. I have seen the phrase "in these days of competitive research" used in a newspaper article on the efforts being made to explain cancer. I think the phrase is unfortunate. It shows the existence of the wrong spirit among those engaged in cancer research, of a desire to make a show, to get out some results, to claim progress when none is being made: in short, it is a phrase coined to fit the spirit of scamped work and hasty conclusions, and it may even be a symptom of a tendency to exploit cancer research for other purposes. I should like to see it possible to substitute the phrase "in these days of coördinated research"; but at the same time contributions to the discussion of cancer banished from lay journals. At the very least, those actually engaged in research should not encourage such contributions.

It will be obvious to you that in so far as the work of the Imperial Cancer Research Fund has been productive of progress, that progress cannot be placed solely to the credit of Dr. Murray, Dr. Cramer, and myself—*i. e.*, to the credit of investigators enjoying the facilities accorded to the Royal Colleges for the pursuit of these investigations. In every direction we have simply gleaned the results of a multitude of willing collaborators at home and abroad without whose aid investigations on the necessary scale would have been impossible. We have had the additional advantage of expert advice from members of subcommittees and have never hesitated to seek further advice at the best sources, both at home and abroad, on matters of importance. It is my firm conviction that it behoves those placing themselves under obligation to devote their whole time to the study of cancer to beware of being

m patient of obtaining results, and that those who supervise or subsidise the investigators must not be in a hurry to see a quick return for the money spent.

On the other hand, a change has come over the methods of investigation and the training and the kind of experience required of the workers themselves. Purely pathological studies are being departed from for experimental and for other methods, requiring the specialist's knowledge of statistics, general biology, chemistry, and physical chemistry to a degree not required of the mere medical man. The posts which would formerly have been filled by pathologists, bacteriologists, and others skilled in the procedures of experimental medicine, are better held by investigators trained in other sciences, but for that reason lacking the attitude of restraint imposed on every member of the medical profession by contact with human suffering. The very reasons leading us to welcome the assistance of other specialists are also reasons for caution, lest too great significance be attached to observations viewed solely in the light of their apparent analogy with normal processes familiar, *e. g.*, to the chemist, the zoologist, or the botanist. Having myself fallen into such an error in formulating a working hypothesis, I trust I may be permitted to voice the necessity for caution.

Workers skilled in the methods of various sciences must learn to appraise the relative value of their respective standpoints, and not hastily conclude that one branch of science has succeeded where another has ignominiously failed. They must control their individual observations by considering them from every standpoint—only so can the rational study of cancer proceed. The facts and the methods of pure pathological anatomy cannot be ignored ; they may be too rashly held to be bankrupt. They constitute the sure and the laboriously laid foundations on which the investigators of the present day are striving to build. The pathologist, the experimentalist, the botanist, the zoologist, the chemist, and those engaged in the application of radioactive agents to the treatment of cancer will be ultimately obliged to bow to the requirements of pathological anatomy. Hence, during this transition stage in the investigation of cancer the representatives of different sciences will do well to take a modest view of their respective capacities and, above all, they must not indulge in "competitive research" but sacrifice themselves to "coördinated investigation," otherwise the investigation of cancer will merely lapse from one state of confusion and error into another.

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